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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/379,540	08/24/1999	SHLOMO BEN HAIM	BIO-76	1397

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EXAMINER	
GHAFOORIAN, ROZ	
ART UNIT	PAPER NUMBER
3763	

DATE MAILED: 05/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/379,540	Applicant(s) HAIM ET AL.	
	Examiner Roz Ghafoorian	Art Unit 3763	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claims 1, 2, 12-15 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S Patent 6283951 to Flaherty et al.

Flaherty discloses systems and methods that use the cardiovascular system as a conduit to deliver drugs, such as therapeutic drugs, genes, growth factors and the like, directly to selected tissue regions within the body. (Col.1, line 10-15) "Drug" as defined herein includes any therapeutic drugs, genetic materials, growth factors, cells, e.g. myocites, vectors carrying growth factors, and similar therapeutic agents or substances that may be delivered within a patient's body for any therapeutic, diagnostic or other procedure. In one aspect of the present invention, a transvascular catheter system is provided that generally includes a catheter, a drug delivery element, an orientation element, and possibly a puncturing element and/or an imaging element. (Col.3 line 54-62)

When the puncturing element is being oriented, the orientation element is imaged. The imaging element is preferably operated to obtain an image of the orientation element in relation to the surrounding tissue, thereby identifying the ordination of the puncturing element because of the predetermined relationship between the orientation element and the puncturing element. (Col.5, lines18-25) This imaging may be considered a sensor; it is a well-known fact that the optical system in the human body is referred to as one of the sensors in the body because it is capable of generating "position and orientation coordinates". The imaging element of this apparatus is also capable to providing position and orientation coordinates information, therefore it could be considered a sensor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 3 --11 rejected under 35 U.S.C. 103(a) as being unpatentable over Flaherty in view of Morocos et al (U.S patent No.5865738). As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Flaherty, however does not teach a method of assessing the viability of the heart. Morocos discloses a method and apparatus for evaluating the viability of a tissue

of interest, particularly that presents as dead but may be merely stunned or hibernating with reduced or no obvious activity, such as contractility (abstract).

This apparatus is carried at the tip of a catheter, which can be guided inside the heart during cardiac catheterization. The new probe allows the physician to: 1) position the probe at a tissue of interest, 2) evaluate the initial state of the tissue, 3) diffuse into the tissue basic ingredients needed for cellular respiration and resulting energy production (oxygen, oxygen-releasing substrates, glucose, low energy phosphates); 4) detect the result of this process by measuring substance uptake, oxygen utilization and/or oxidation reduction (redox) stores of the respiratory enzymes; and 4) optionally detect consequent mechanical activity by ultrasound backscatter technique (in conjunction with a second catheter). (col.9, line 31) This apparatus allows a one to plan in detail (definition of mapping as found in dictionary was plan in detail) where the damaged tissue was located, and when a myocite or a myoblast should be delivered. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combine the two teaching, since according to Morocos cardiologists and cardiac surgeons would both benefit from a procedure which would identify cardiac tissue which has a good probability of returning to normal function. (Col.5, line 60) Faced with the recognition of widened variety of ischemic clinical pictures with variable degree of retained viability, and armed with the knowledge that several conditions previously considered hopeless can now be salvaged if appropriately recognized as viable, cardiologists and cardiac surgeons are increasingly aware of the

need to optimize selection form their ever-widening choice of techniques in a way that matches the particular clinical situation. (Col.2 line 10-20)

2. Claims 16-17, 25-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flahetry as applied to claim1 above, and further in view of Gambale et al U.S Patent No.6277082. As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Flaherty, however, does not teach a catheter which utilizes a laser to create a channel at an oblique angel were the said cells would be delivered. Gambale discloses an invention provides devices and methods for detection of ischemic biological tissue by temporarily altering the temperature of the tissue. (Abstract) Gambale also discloses a detection of an ischemic area of tissue may be followed by a treatment, which may include the implantation of an angiogenic implant alone or in conjunction with a therapeutic agent, such as a growth factor to promote angiogenesis or a cell or gene therapy substance to initiate regeneration of the subject tissue. In such cases, the obturator is adapted to penetrate the tissue in order to facilitate the placement of the angiogenic implant into the tissue alternatively the treatment may comprise creation of channels in the ischemic region by mechanical or laser energy.(col. 3 , line 40-50) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of both Flaherty and Gambale, because according to Gambale if the tissue has remained viable despite the previous deprivation of blood, revascularization, or the

restoration of blood flow, to dormant or hibernating tissue can restore the muscle's normal function. (Col.1, line 5-10) Injection of growth factor into myocardial tissue initiates angiogenesis at that site, which is exhibited by a new dense capillary network within the tissue accurate diagnosis and identification of ischemic areas is essential to proper treatment. (Col.2, Line 5-25)

3. Claims 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flaherty in view of U.S Patent No. 6277082 to Gambale and further in view of German et al U.S Patent No.6258789. As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Gambale discloses an ischemia detection system. However, neither Gambale nor Flaherty teaches the origin of the cell. German discloses cells of a mammalian subject, which are genetically altered to operatively incorporate a gene, which expresses a protein, which has a desired effect. (Abstract). One of the objects of German's method is to produce genetically transformed cells (genetically superior cell), which have incorporated in the their genome exogenous genetic material in the form of a fully functional gene which expresses biologically active and therapeutically useful protein that functions with in the cell. (col.3, line 34-39) any exposure of the DNA of the treated cell to the immune system can result in adverse reaction such as inflammatory reactions to the DNA administered. (Col.2 lines 53-60) Therefore, it would be beneficial to treat these cells with immunosuppressants prior to implantation.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of Gambale, Flaherty and German, because German simply expands on the origins of the cells in Flaherty and Gambale teachings. German is not specifically speaking of myocites, but nor are any of the claims 18-20.

4. Claim 33, 36, 39 rejected under 35 U.S.C. 103(a) as being unpatentable over Flahery in view of Gambale, and further in view of Kramer U.S Patent No.5960796. As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Gambale discloses an ischemia detection system. However, neither Gambale nor Flaherty teaches a catheter with a device capable of providing a pressure burst. Kramer discloses a method of infusion of drug in to the bone marrow. It also teaches a monitoring over pressurization during high-pressure infusions or blocked fluid flow. These operations could be combined with a microprocessor-controlled system to automatically warn the operator of unsafe or otherwise unsatisfactory conditions. (Col.4, line 40) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of Gambale, Flaherty and Kramer, because according to Kremer this invention helps in monitoring over pressurization. Although Kramer's apparatus is for the use of the bone marrow but it is the concept behind a safety valve to monitor pressure that is relevant

here. Kramer teaches why it would be important to utilize a pressure bust in any system not just in the bone marrow.

5. Claims 34, 37, 40 are under 35 U.S.C. 103(a) as being unpatentable over Flahery in view of Gambale, and further in view of Lemelson U.S Patent No.4578061. As noted above, the Flaherty reference discloses a drug delivery device, which consists of a catheter, one position sensor, and delivers cells such as myoblasts or myocyte in to the heart chamber. Gambale discloses an ischemia detection system. However, neither Gambale nor Flaherty teaches teach a catheter with a retractable needle. Lemelson discloses a catheter with a retractable needle and method are provided for injecting a quantity of a liquid. (Abstract) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention as made to have included the teaching of Gambale, Flaherty and Lemelson, because according to Lemelson the needle need to be retractable so that it will not penetrate tissue as the device is worked through the body. (Col.1 line 40)

Response to Arguments

6. Applicant's arguments filed 15 March 2002 have been fully considered but they are not persuasive.

a. The applicant has amended claim 1 and has add "to generate position and orientation coordinates." The applicant further traverses the rejection because according to the applicant the "orientation element" is incapable of being used as a position sensor, which generates signals responsive to the position of the catheter.

The point the applicant makes about the "orientation element" is valid but Flaherty contains both an orientation element as well as an imaging element. And the imaging element is capable of being used as a position sensor, which generates signals responsive to the position of the catheter.

It is a well-known fact that the optical system in the human body is referred to as one of the sensors in the body because it is capable of generating "position and orientation coordinates". The imaging element of this apparatus is also capable to providing position and orientation coordinates information, therefore it could be considered a sensor.

b. The applicant traverse all of the 103 rejections on the bases that none of cited prior art references, either alone or in combination, described, suggest or infer a method for delivering a cell to a heart of a patient comprising the steps of providing an apparatus for intracardiac drug administration comprising a catheter wherein the catheter has at least one position sensor which generates signals responsive to the position of the catheter and the signals are used to generate position and orientation coordinated, and a drug delivery device for delivering the cell; inserting the catheter into a chamber of the heart at a site; and delivering the cell to the site with the drug delivery device based on position ad orientation coordinates in response to the signals form the position sensor.

i. Claims 3-11 were rejected by Flaherty in view of Morocos et al: Morocos teaches the method of detection of viable tissue in *the heart* of the patients, and describes several reasons why it would be beneficial to know the status of the tissue. And one of the reasons given by Morocos is that caregivers are armed with the knowledge that several conditions previously considered hopeless can be salvaged. It is true that Morocos

does not disclose intracardiac drug administration specifically but in order to treat the damaged tissue in Flaherty's reference, the care giver must know where to target the treatment and Morocos's apparatus provides the toll in helping the caregiver to target the damaged tissue.

ii. Claims 16-17, 25-31 were rejected by Flaherty in view of Gambale: Gambale teaches the method and apparatus for detecting ischemic biological tissue. It further teaches in all of its embodiments, detection of an ischemic area of tissue maybe followed by a treatment, which may include the implantation of an antigenic implant alone or in conjunction with a therapeutic agent, such as growth factor or promote angiogensis or a cell or gene therapy substance to imitated regeneration of the subject tissue. Gambale does not discuss the method of placing the cells in to the ischemic detected tissue but it is clear that Gambale supports the idea of a method in which it is necessary to identifying an ischemic tissue prior to the interacardial treatment.

iii. Claims 19-24 were rejected by Flaherty in view of Gambale and further in view of German: German teaches the delivery of gene products by cell expression. German does concentrate on cells of the intestine and not the heart cells, but it does point out, protein drugs have been used to treat disease such as cancer, hemophilia, anemia, and diabetes. (Col.1,

lines 15-20) German also teaches that protein drugs have limited use by several restrictive technical factors. First, proteins remain difficult and expensive to manufacture compared to other drugs. Large-scale purification of proteins in bioactive form can be a limitation step in the commercialization of these drugs. Second, many proteins are metabolized or otherwise eliminated quickly in the patient. This results in the need for frequent re-administration. Delivery of therapeutic gene products by expression in cell transformed with a therapeutic gene product-encoding DNA has attracted wide attention as a method to treat various mammalian disease and enhance production of specific protein or other cellular products. This promising technology often refers to as gene therapy. (Col.1, lines 25-40) Although German applies this information for gene therapy in the cells of Gastrointestinal system, there is no limitation for the use of this information in any of the organ systems of the body. As mentioned above protein drugs have helped in cancers, anemia, hemophilia, diabetes's, and many other types of illnesses, so why not use gene therapy instead of the problematic drugs to help with this illness. Therefore it would have been beneficial in Flaherty's gene therapy to modify the DNA of the cells being implanted to make them genetically superior cells, by allowing them to express proteins which enhance angiogenesis, which normally would not be expressed by the implanted cell.

German further teaches that exposure of the DNA of above mentioned gene's to the immune system will result in an adverse reaction. (Col.2, lines 56-61) Therefore, it would be obvious to want to either treat the cells used in gene therapy with an immunosuppressent or to suppress the patient's own immune system. If one was to suppress the patient's immune system, the patient would become neutropenic and chances of mortality and morbidity would increase dramatically, which would lead to a much greater chance of the patient dying of the gene therapy procedure rather than there underlying congestive heart failure.

iv. Claims 33, 36, and 39 were rejected by Flaherty in view of Gambale and further in view of Kramer: Kramer teaches an implantable interaosseious device for rapid vascular access. Kramer teaches by monitoring pressure while infusion of drugs or other material may prevent potentially dangerous situations, including over pressurization during high-pressure infusions or locked fluid flow. (Col.4, lines 30-35) Kramer points out why it would be beneficial to use a pressure bust in any procedure that requires infusion of material in to the body.

v. Claims 34, 37, and 40 were rejected by Flaherty in view of Gambale, and further in view of Lemelson: Lemelson teaches an injection catheter and method. Lemelson disclose that the needle of the catheter is

retractable so that it will not penetrate tissue as the device is worked though the body ducts. (Col.1, lines 40-45) Lemelson points out why it would be necessary to use a retractable needle in any device that would be inserted in the body.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roz Ghafoorian whose telephone number is 703-305-2336. The examiner can normally be reached on 8:30am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Casler can be reached on 703-308-3552. .

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0858.

RG
April 5, 2002

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